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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/622,452	10/31/2000	David B. Weiner	UPAP0011-100	6483

34137 7590 07/17/2009

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
07/17/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/622,452	WEINER ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,6,7,9-12,15,17,18,33,36,42,43,46,49,50 and 52-58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,6,7,9-12,15,17,18,33,36,42,43,46,49,50 and 52-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/1/09, 6/1/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/30/09 and the accompanying amendment and response have been entered. Claims 2-3, 5, 8, 13-14, 16, 19-32, 34-35, 37-41, 44-45, 47-48, and 51 are canceled, and new claims 56-58 have been added. Please note that although applicant's remarks state that claim 46 has been canceled, the actual amended claim set filed on 4/30/09 shows claim 46 as pending and "previously presented", and claim 47 as canceled. Thus, claims 1, 4, 6-7, 9-12, 15, 17-18, 33, 36, 42-43, 46, 49-50, and 52-58 are currently pending and under examination in the instant application. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in the previous office action.

Claim Rejections - 35 USC 102

Claims 1, 6, 12, 17, and 53-54 stand rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,417,328 (7/9/02), hereafter referred to as Alnemri. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the rejection of record for reasons of record as discussed in detail below..

The applicant reiterates their previous argument that Alnemri et al. does not teach a "pyrogen free" composition, and that while Alnemri teaches "expressible nucleic acids encoding DR5", the current claims recite a plasmid comprising a nucleic acid encoding DR5 and not an "expressible nucleic acid encoding DR5". In response, Alnemri et al. clearly teaches a plasmid encoding DR5 and the immunogen LacZ, which is a bacterial antigen, or the combination of the plasmid encoding DR5 and the plasmid encoding CrmA, a viral protein antigen, and further provides teachings for making a sterile aqueous solution in columns 22-23. Note that as there is no requirement that the a prior art reference must set forth the claimed invention *in haec verba,* it is irrelevant that Alnemri et al. does not use the phrase "pyrogen free" as Alnemri et al. clearly teaches sterile aqueous solutions of the disclosed plasmids which meet the definition of "pyrogen free", as discussed in detail below and in previous office actions.

The applicant further argues that a reading of the section in Alnemri about physiological carriers, i.e. columns 22-23, has nothing to do with the disclosure elsewhere in the document of reagents for experimentation. This is not agreed. The disclosure in column 22 concerning therapeutic compositions of DR5 refers specifically to "expressible nucleic acids encoding DR5". As stated in previous office actions, the plasmids exemplified in columns 27-28 are in fact expressible nucleic acids. Further, Alnemri broadly teaches to prepare "expressible nucleic acids encoding DR5" as sterile aqueous solutions that do not contain any material other than the nucleic acid and water or physiological saline (column 23, lines 12-17). As such, the teachings in columns 22-23 to prepare sterile aqueous solutions of the nucleic acids reads on the particular plasmids disclosed in the examples. Also, as stated in previous office actions, a sterile aqueous solution that does not contain any material other than the nucleic acid and water or physiological

saline appears to qualify as "pyrogen-free" absent evidence to the contrary. Therefore, for reasons of record as discussed in detail above, the rejection stands.

Claim Rejections - 35 USC § 103

The rejection of claims 1, 6, 12, 17 and 53-54 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,417,328 (7/9/02), hereafter referred to as Alnemri, in view of U.S. Patent No. 5,693,622 (12/2/97), hereafter referred to as Wolff et al. is maintained. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the rejection of record for reasons of record as discussed in detail below.

The applicant reiterates their previous arguments that there is no motivation to make a pyrogen free plasmid encoding DR5 in either Alnemri or Wolff. In response, Alnemri specification broadly teaches to prepare "expressible nucleic acids encoding DR5" as sterile aqueous solutions that do not contain any material other than the nucleic acid, water or physiological saline. Thus the teachings in column 22 to prepare sterile aqueous solutions of the nucleic acids reads on the particular plasmids disclosed in the examples, which include a single plasmid encoding DR5 and the bacterial pathogen immunogen LacZ or the combination of a plasmid encoding DR5 and a plasmid encoding CrmA, a viral pathogen antigen, regardless of whether they were actually used in *in vitro* experiments versus *in vivo* methods. Therefore, in view of teachings of Alnemri et al. to prepare a sterile pharmaceutical composition comprising a plasmid(s) encoding DR5 for administration to a mammal, and the teachings of Wolff et al. for standard methods of preparing plasmid DNA, it would have been *prima facie* obvious to the

skilled artisan at the time of filing to use the well known and widely practiced methods taught by Wolff et al. to prepare the plasmids encoding DR5 and an immunogen taught by Alnemri et al.. Further, based on the standard nature of cesium chloride purification, and the high level of skill in the art of molecular biology at the time of filing, the skilled artisan would have had a reasonable expectation of success in producing a pyrogen-free composition containing the plasmid(s) taught by Alnemri et al. using the purification method taught by Wolff et al. Therefore, the rejection of record is maintained.

Claim Rejections - 35 USC 112

The rejection of claims 1-4, 6-7, 9-15, 17-18, 33-36, 40-45, 47-48, and 50-52 under 35 U.S.C. 112, first paragraph, for scope of enablement, is maintained over currently pending claim 11 and withdrawn over pending or canceled claims 1, 4, 6-7, 9-10, 12, 15, 17-18, 33, 36, 42-44, and 46-55. Applicant's amendments and arguments have been fully considered but have not found persuasive in overcoming the grounds of rejection for reasons of record as discussed in detail below.

In regards to pending and new claims 1, 4, 6-7, 9-10, 12, 15, 17-18, 33, 36, 42-43, 46, 49-50, and 52-58, the examiner finds that 1) the specification provides sufficient enabling guidance to make a product composition comprising a one or two plasmids comprising a nucleotide sequence encoding a pathogen immunogen and a nucleotide sequence encoding DR5, and 2) that although the specification as supported by the Declaration under 37 CFR 1.132 by David Weiner filed previously on 1/20/06 provides evidence that the intramuscular administration of plasmids

encoding either an HIV antigen or an Influenza antigen and DR5 can induce antigen specific CTL, the specification does not provide an enabling disclosure for the immunization against any pathogenic disease including viral diseases, other than Influenza. Claims 1, 4, 6-7, 9-10, 12, 15, 17-18, 33, 36, 42-43, 46, 49-50, and 52-58 are either product claims, or methods of inducing a CD8+ T cell response through intramuscular injection of either one or two plasmids comprising nucleotide sequences encoding a pathogen antigen and DR5, and more specifically an HIV, HSV, or Influenza antigen. None of these claims recites a particular therapeutic outcome, such as immunization or treatment, on any pathogenic disease. As such, these claims have been found to be enabled in view of the elected species of DR5.

However, claim 11 continues to recite a method of immunizing an individual against HSV. Applicant's arguments have not been found persuasive in overcoming the rejection of record for the lack of enablement for immunizing any individual against HSV by intramuscular administration of one or two plasmids encoding an HSV antigen and DR5. The previous office actions stated that the specification, while being enabling for a method of immunizing a mammal against Influenza comprising co-administering a plasmid DNA encoding Influenza HA and a plasmid encoding DR5 by intramuscular injection, does not reasonably provide enablement for methods of immunizing against any pathogen by administering plasmid(s) encoding an immunogen and DR5. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The applicant argues that the skilled artisan would not accept that the evidence of record shows the unpredictability of achieving an antiviral effect by generating antigen specific CD8+ T

cells. The applicant also argues that at the time of the invention one of skill in the art could make and use DNA vaccines and the specification describes how DR5 can act as an adjuvant in a DNA vaccine protocol. The applicant also states that the degree to which an immune response generated is protective is not an element of the claims, that the claims do not refer to protective immune responses, and that cytotoxic T cells may have antiviral activities despite not providing protection against infection. In response, please note that claim 11 is drawn to a method of immunizing an individual against HSV, i.e. generating a protective immune response against HSV. Thus, applicant's argument is not persuasive as the claim as written does in fact read on the generation of immune responses which are capable of preventing or reducing infection with HSV. Further, the Declaratory evidence previously provided and analyzed in detail in previous office actions is not commensurate in scope with the instant claim and does not teach or suggest that the co-administration of plasmid encoding DR5 has any effect on B cell responses, or any other immune effector cell responses other than CD8+ T cell responses, and the prior art of record teaches that the generation of antigen specific CD8+ T cells does not predictably correlate with a treatment effect on viral infections (see Yasutomi et al., Erdile et al., and Ertl et al.). It is further noted that while the declaratory evidence did in fact demonstrate a correlation between the generation of Influenza HA specific CTL by intramuscular injection of plasmid encoding HA and DR5, no such correlation was demonstrated for HSV antigen specific CTL.

Therefore, in view of the state of the art of generating therapeutic immune responses at the time of filing, the limitation of the declaratory evidence to a showing that DR5 can enhance CD8+ T cell responses to Influenza antigens using intramuscular injection, the art recognized unpredictability in immunizing against any pathogenic disease by generating a CD8+ T cell

response, and the breadth of the claim, it would have required undue experimentation to practice the method as claimed in claim 11.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 33, 36, 52, and 55-58 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Independent claims 33 and 56 lack antecedent basis for the first recitation of "said immunomodulating protein". Claims 36, 52, 55, and 57-58 depend on either claim 33 or claim 56 and thus are included in this rejection.

Claim Objections

The objection to pending claims 1, 4, 6-7, 9-12, 15, 17-18, 33, 36, 42-43, 46, 49-50, and 52-58 for continuing to recite non-elected subject matter, there being no allowable generic claim, is maintained. Note that all pending claims are in fact generic. The applicant argues that all the claims recite the elected species and that once this species is found to be allowable that the generic claims and a reasonable number of non-elected species be examined and allowed. In response, it is first noted that the instant claims have not been found allowable based on examination of the elected species of DR5. Further, MPEP 809.02(a) states:

> Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

As the generic claims have not been found allowable, see below, the objection to the claims remains.

In the interests of compact prosecution it is noted that should applicant limit the claims to the elected subject matter of DR5, fix the antecedent basis problems for claims 33, 36, 52, and 55-58 identified above, and rewrite all claims dependent on rejected claims 1, 6, and 12 in independent form, the subject matter of claims 4, 7, 9-10, 15, 18, 33, 36, 42-43, 46, 49-50, 52, and 55-58 would be considered free of the prior art of record and allowable.

Applicant is further advised that should claim 7 be found allowable, claim 33 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

The following rejections are made of record to demonstrate that none of the generic claims are allowable. Please note that the election of species requirement has NOT been withdrawn, and full examination of the claims remains based on the elected species of DR5 as the immunomodulatory molecule.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 6-7, 12, 17-18, 33, and 53-57 are rejected under 35 U.S.C 102(b) as being anticipated by WO 96/36366 (1996), hereafter referred to as Dow et al.

Dow et al. teaches compositions and pharmaceutical compositions comprising a single plasmid comprising a nucleotide sequence encoding a superantigen immunogen or other immunogen operably linked to transcriptional regulatory sequences and a nucleotide sequence encoding a chemokine operably linked to regulatory sequences, or two separate plasmids where a first plasmid comprises a nucleotide sequence encoding a superantigen immunogen or other immunogen operably linked to transcriptional regulatory sequences and a second plasmid comprises a nucleotide sequence encoding a chemokine operably linked to regulatory sequences (Dow et al., pages 22-23, 53-55, and 104-126). Dow et al. further teaches the plasmid(s) where the immunogen is a viral or bacterial immunogen, and where the chemokine is preferably MIP-1α or MIP-1β, MCP-1, IL-8, or RANTES (Dow et al., pages 14, 53-55, and 104-126). In addition, Dow et al. teaches the intramuscular injection of plasmid(s) encoding an immunogen and a chemokine such as MIP-1α or MIP-1β, MCP-1, IL-8, or RANTES to an individual to induce and/or enhance immunogen specific immune responses and in particular CTL responses to the immunogen (Dow et al., pages 88-93). Finally, Dow et al. teaches the preparation of the plasmids for injection into an individual where the plasmid(s) are purified by cesium chloride

gradient centrifugation and resuspended in sterile PBS (Dow et al., page 89). Note that cesium chloride gradient centrifugation removes bacterial contaminants such that resuspension of the isolated plasmid DNA in sterile water produces a pyrogen free composition. Thus, by teaching all the limitations of the claims as written, Dow et al. anticipates the generic claims of the instant invention.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 4, 9-11, 15, 36, 42-43, 46, 49-50, 52, and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/36366 (1996), hereafter referred to as Dow et al., in view of US Patent 6,204,250 (2001), hereafter referred to as Bot et al., and US Patent No. 5,494,807 (1996), hereafter referred to as Paoletti et al.

Dow et al. teaches compositions and pharmaceutical compositions comprising a single plasmid comprising a nucleotide sequence encoding a superantigen immunogen or other immunogen operably linked to transcriptional regulatory sequences and a nucleotide sequence encoding a chemokine operably linked to regulatory sequences, or two separate plasmids where a first plasmid comprises a nucleotide sequence encoding a superantigen immunogen or other immunogen operably linked to transcriptional regulatory sequences and a second plasmid comprises a nucleotide sequence encoding a chemokine operably linked to regulatory sequences (Dow et al., pages 22-23, 53-55, and 104-126). Dow et al. further teaches the plasmid(s) where

the immunogen is a viral or bacterial immunogen, and where the chemokine is preferably MIP-1α or MIP-1β, MCP-1, IL-8, or RANTES (Dow et al., pages 14, 53-55, and 104-126). In addition, Dow et al. teaches the intramuscular injection of plasmid(s) encoding an immunogen and a chemokine such as MIP-1α or MIP-1β, MCP-1, IL-8, or RANTES to an individual to induce and/or enhance immunogen specific immune responses and in particular CTL responses to the immunogen (Dow et al., pages 88-93). Finally, Dow et al. teaches the preparation of the plasmids for injection into an individual where the plasmid(s) are purified by cesium chloride gradient centrifugation and resuspended in sterile PBS (Dow et al., page 89). Note that cesium chloride gradient centrifugation removes bacterial contaminants such that resuspension of the isolated plasmid DNA in sterile water produces a pyrogen free composition.

Dow et al. teaches all limitations of the generic claims except for the use of plasmids encoding specific viral immunogens such as an Influenza immunogen, an HIV immunogen, or an HSV-2 gD immunogen. Bot et al. supplements Dow et al. by teaching that various plasmids encoding viral antigens derived from Influenza virus, HIV, or HSV-2 operably linked to transcriptional control sequences and administered intramuscularly can be used to generate antigen specific CTL and immunize adults and infants against viral diseases such as Influenza and HSV (Bot et al., columns 4, 6-9, and 29-30, and specifically claims 1-19). Therefore, in view of teachings of Dow et al. to make and use one or two plasmid DNAs encoding a viral immunogen and a chemokine for the generation and enhancement of CTL by intramuscular injection, and the specific teachings of Bot et al. that plasmids encoding viral antigens from HIV, HSV-2, and Influenza can be used successfully to generate CTL through intramuscular injection, it would have been *prima facie* obvious to the skilled artisan at the time of filing to utilize an

HIV, HSV-2, or Influenza immunogen as taught by Bot et al. in the plasmid compositions of Dow et al. and in the methods of generating CTL responses taught by Dow et al. with a reasonable expectation of success.

Dow et al. and Bot et al., while teaching plasmids encoding viral immunogens, and specifically viral immunogens derived from HSV-2, do not specifically teach the use of the HSV-2 gD immunogen for generating CD8+ T cell responses. However, at the time of filing, the HSV-2 gD antigen was well known as evidenced by Paoletti et al. who teaches immunogenic compositions comprising nucleic acids encoding the HSV-2 gD immunogen (Paoletti et al., columns 33-36, and 431-434). Therefore, in view of teachings of Dow et al. to make and use one or two plasmid DNAs encoding a viral immunogen and a chemokine for the generation and enhancement of CTL by intramuscular injection, the specific teachings of Bot et al. that plasmids encoding viral antigens HSV-2 can be used successfully to generate CTL through intramuscular injection, and the teachings of Paoletti et al. that HSV-2 gD is an HSV-2 immunogen useful in nucleic acid based immunization, it would have been *prima facie* obvious to the skilled artisan at the time of filing to utilize a nucleic acid encoding HSV-2 gD as taught by Paoletti et al. in the plasmid compositions of Dow et al. and in the methods of generating CTL responses taught by Dow et al. with a reasonable expectation of success.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. If the examiner is not

available, the examiner's supervisor, Joseph Woitach, can be reached at (571) 272-0739. For all official communications, the technology center fax number is (571) 273-8300. Please note that all official communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for electronic images of applications. For questions or problems related to PAIR, please call the USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197. Representatives are available daily from 6am to midnight (EST). When calling please have your application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

/Anne Marie S. Wehbé/
Primary Examiner, A.U. 1633